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(71) Applicant *(for all designated States except US)*: THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BARRETT, David, Michael [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham NG2 3AA (GB). JONES, Huw, Lyn [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham NG2 3AA (GB). JONES, Idwal [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham NG2 3AA (GB). SMITH, Carl, Simon [GB/GB]; The Boots Company PLC, 1 Thane Road West, Nottingham NG2 3AA (GB).

(74) Agent: THACKER, Michael, Anthony; The Boots Company PLC, Group Patents Dept., D31, 1 Thane Road West, Nottingham NG2 3AA (GB).

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(57) Abstract

The present invention relates to the use of an NSAID selected from ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin in the treatment of the symptom of cold and flu particularly sore throat which comprises the administration to a patient in need of such treatment of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or a spray containing a therapeutically effective amount of the NSAID which releases the NSAID in the oral cavity so as to deliver the NSAID to the surface of the sore throat. The composition may also contain (a) therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn–masking amount of an agent which has a warming effect on the mucosa of the throat.

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PHARMACEUTICAL COMPOSITIONS

The present invention relates to pharmaceutical compositions containing certain non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs also having analgesic and antipyretic activity. The invention also relates to the use of these new pharmaceutical formulations in the treatment of the symptoms of cold and flu particularly sore throat. Some NSAID molecules exist in two enantiomeric forms and the term NSAID as used herein is intended to embrace the individual enantiomers and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as the racemic form. NSAIDs can exist in the form of pharmaceutically acceptable salts or in the form of derivatives such as esters and such salts or esters are embraced by the term "NSAID" as used herein.

A first aspect of the present invention provides the use of an NSAID selected from ketoprofen, diclofenac, piroxicam and indomethacin in the treatment of sore throats which use comprises the administration to a patient in need of such treatment of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or a spray containing a therapeutically effective amount of said NSAID which releases the said NSAID in the oral cavity so as to deliver the said NSAID to the surface of the sore throat.

A further aspect of the present invention provides pharmaceutical compositions comprising a combination of a therapeutically effective amount of an NSAID selected from ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin with a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral

compound, an antibiotic compound, an antifungal compound, minerals and vitamins in the form of a masticable or suckable solid dosage form or a liquid or a spray.

Suitable antihistamines include acrivastine, azatadine, buclizine, cetirizine, cinnarizine, clemastine, loratidine and pharmaceutically acceptable salts thereof.

Suitable cough suppressants include codeine, dextromethorphan or pholcodine and pharmaceutically acceptable salts thereof.

Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine and pharmaceutically acceptable salts thereof.

Suitable expectorant include acetylcysteine, ammonium chloride, carbocysteine, guaifensin and potassium citrate.

A suitable muscle relaxant is methocarbamol.

Suitable centrally acting analgesics include codeine and its salts and hydrocodone.

Suitable local anaesthetics include benzocaine, lignocaine, mepivacaine, prilocaine and pharmaceutically acceptable salts thereof.

Suitable antibacterial compounds include amylmetacresol, dichlorobenzyl alcohol, quaternary ammonium compounds such as cetrimide, or benzalkonium chloride.

Suitable antiviral compounds include zinc salts (for example the acetate, gluconate and ascorbate salts), acyclovir and its sodium salt.

A suitable antibiotic is metronidazole.

Suitable antifungal compounds include nystatin, amphotericin, imidazoles such as miconazole and triazoles such as fluconazole.

Suitable minerals include zinc and selenium salts.

Suitable vitamins include vitamins A, C, D, E and K, sodium ascorbate, riboflavine and thiamine hydrochloride.

The above mentioned active ingredients are well known in the field of pharmacy and the dose of each to be given can be found from standard reference books. See for example Martindale The Extra Pharmacopoeia 29th Edition published by The Pharmaceutical Press the disclosure of which is herein incorporated by reference.

A further aspect of the present invention provides pharmaceutical compositions comprising a combination of a therapeutically effective amount of an NSAID selected from ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin with a burn-masking amount of an agent which has a warming effect on the mucosa of the throat in the form of a masticable or suckable solid dosage form or a liquid or a spray. Suitable warming agents include ginger, chilli and agents containing or consisting of anethole.

Anethole (1-methoxy-4-(1-propenyl)benzene or p-propenylanisole) is found naturally as the chief constituent of anise oil, star anise oil and fennel oil. It can be incorporated into the compositions in the present invention in substantially pure form, produced either by extraction from the above oils or

synthetically, or it may be incorporated as one of the above oils. The amount of anethole should be such that the required amount of taste masking is obtained.

The compositions of the present invention are intended for use in the treatment of the symptoms of colds and flu particularly sore throat by the administration to a patient in need thereof of a pharmaceutical composition according to the present invention in the form of a masticable or suckable solid dosage form or a liquid or a spray containing a therapeutically effective amount of said NSAID which releases the said NSAID and any active ingredient and/or burn-masking agent that is present in the oral cavity so as to deliver the said NSAID, active ingredient(s) and/or burn-masking agent to the surface of the sore throat.

The solid dosage form may be a lozenge which is intended to be sucked by the patient or a masticable or suckable tablet, capsule, pastille or gum, for example chewing gum. The term "lozenge" as used herein is intended to embrace all dosage forms where the product is formed by cooling a sugar-based or sugar alcohol based (eg isomalt) molten mass containing the active material. The term "tablet" as used herein is intended to embrace unit dosage forms made from compressed powders or granules or compressed pastes. A preferred pharmaceutical composition is a lozenge prepared by cooling a heated lozenge base containing the NSAID, active ingredient(s) and/or burn-masking agent and other excipients to form solid lozenges.

The therapeutically effective amount of the NSAID when given in the absence of any other active ingredients has been found to be from 5% to 40% of the normal adult dose when given by ingestion to achieve a systemic antiinflammatory and/or analgesic effect. The NSAID may therefore be present in the pharmaceutical composition in an amount from 2.5 to 25 mg preferably 5 to 12.5 mg. Where a pharmaceutically acceptable salt of the

NSAID is used, the amount of the salt used should be such as to provide the desired amount of NSAID. Suitable salts include the alkali metal salts eg the sodium salt or amino acid salts eg the lysine, arginine or meglumine salts. Suitably the dose of piroxicam is in the range 15 to 25 mg, preferably 20 mg, the dose of ketoprofen is 10 to 15 mg, preferably 12.5 mg, the dose of indomethacin is 5 to 10 mg, preferably 6 mg and the dose of diclofenac (in the form of its sodium salt) is 5 to 10 mg, preferably 6.25 mg.

When the NSAID is used in combination with one or more of the active ingredients listed above, the amount of NSAID present may be in the range 2.5 to 200 mg. The preferred amounts of the NSAIDs listed above are as given above. Suitably the dose of ibuprofen or naproxen is in the range 50 to 200 mg when used in combination with one or more of the active ingredients listed above.

NSAIDs would be expected to cause an unpleasant burning sensation at the back of the mouth when retained in the mouth. This would clearly be unacceptable to the patient being treated. The present applicants have surprisingly found that an unacceptable burning sensation is not experienced when the present invention is used to treat a sore throat but that the patient does receive relief of the symptoms of the sore throat.

Solid dosage forms may be prepared by methods which are well known in the art for the production of lozenges, tablets, capsules or chewing gums and may contain other ingredients known in such dosage forms such as acidity regulators, opacifiers, stabilising agents, buffering agents, flavourings, sweeteners, colouring agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. Any additional ingredient which is added should not react with any other component of the pharmaceutical compositions of the present invention. If such interactions are possible the components concerned should be kept separate for example by encapsulating

one or both of the possibly reacting components, by including one of the components in a coating applied to the lozenge after manufacture or by having the components in different layers of a multilayer product. For example, if the flavour or component of the flavour or an excipient or carrier for the flavour contains an alcohol moiety, there is the possibility of esterification of the carboxylic acid moiety in the phenylpropionic acid NSAIDs. Such esterification can be prevented or minimised by the methods outline above.

The preferred solid formulations of the present invention may be prepared as lozenges by heating the lozenge base under vacuum to remove excess water. The lozenge base may be a sugar-based or sugar alcohol-based composition. If the lozenge base is sugar-based, it may comprise a single sugar (eg sucrose) or a mixture of sugars (eg a mixture of sucrose and glucose). If the lozenge base is sugar-alcohol based it may comprise sorbitol, xylitol, maltitol, maltitol syrup, lactitol, mannitol or mixtures thereof which may be in the form of the free sugar alcohols, derivatives thereof or mixtures thereof. One preferred lozenge base comprises an approximately equimolar mixture of alpha-D-glucopyranosyl-1,6-D-sorbitol and alpha-D-glucosopyranosyl-1,1-D-mannitol (isomalt) optionally in conjunction with a hydrogenated glucose syrup such as lycasin. The lozenge base is preferably heated to a temperature in the range 110 to 170°C under vacuum to remove water to give a moisture content which is preferably less than 2%, more preferably less than 1% before the remaining components of the pharmaceutical lozenge formulation are added. The remaining ingredients may be blended into the lozenge base mixture as powders or liquids. Powders may be granulated prior to the mixing step. The molten mixture may then be passed to individual moulds in which each lozenge is formed or may be drawn into a continuous cylindrical mass from which the individual lozenges are formed. The lozenges are then cooled, subjected to a visual check and packed into suitable packaging. One form of suitable packaging is a blister pack of a water-impermeable plastics material (eg polyvinylchloride) closed by

a metallic eg aluminium foil. The patient removes the lozenge by applying pressure to the blister to force the lozenge to rupture and pass through the metal foil seal. Lozenges will normally be sucked by the patient to release the NSAID.

Masticable solid dose formulations may be made by the methods used to prepare chewable candy products or chewing gums. For example, a chewable solid dosage form may be prepared from an extruded mixture of sugar and glucose syrup to which the NSAID has been added with optional addition of whipping agents, humectants, lubricants, flavours and colourings. (See Pharmaceutical Dosage Forms: Tablets, Volume 1, Second Edition edited by H A Lieberman, L Lachman and J B Schwartz published in 1989).

Liquid and spray formulations may be prepared by dissolving or suspending the NSAID in a liquid medium which may also contain other ingredients such as stabilising agents, buffering agents, flavourings, sweeteners, colouring agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. The formulation may then be packaged into an appropriate container. For example, a spray may be prepared by dissolving water soluble components in water and non-water soluble ingredients in a co-solvent (eg alcohol). The two phases are then mixed and the resulting mixture filtered and placed into dispensing containers. The dispensing containers may be fitted with a metered, manually-operated spray mechanism or the dispenser may contain a pressurised propellant and be fitted with a suitable dispensing valve.

One form of preferred formulations for use in the present invention are compositions which can be sucked or chewed by the patient and which slowly release the NSAID and any active ingredient and/or burn-masking agent. The NSAID, active ingredient and/or burn-masking agent then passes over the mucous membrane of the throat where some is absorbed providing topical

relief. The unabsorbed NSAID and active ingredient is then ingested by the patient and absorbed into the blood stream. The NSAID and active ingredient so absorbed can act systematically in addition to the relief that comes from the topical application of NSAID and active ingredient to the mucous membrane of the throat.

A second form of preferred formulations for use in the present invention are sprays which are administered so that the liquid composition is brought into contact with the mucus membrane of the throat so that some of the active components of the composition (NSAID and other active ingredients and/or burn-masking agent) is absorbed providing topical relief. Ingestion of the remainder of the liquid composition then means that the unabsorbed NSAID and active ingredient can be absorbed in to the blood stream to provide systemic relief in addition to the relief that comes from the topical application of the NSAID and active ingredient to the mucous membrane of the throat.

The invention will be illustrated by the following Examples which are given by way of example only.

Example 1

Lozenges containing racemic ketoprofen (12.5 mg per lozenge) were prepared by heating the solids from a 1:1 mixture of sugar and liquid glucose to 140° and applying a vacuum to reduce the water content of the mixture. The NSAID was added and the resulting mixture was cooled and formed into a continuous cylindrical mass from which the individual lozenges were formed each weighing 2350 mg. The individual solid lozenges were visually inspected and then packed.

The resulting lozenges were found to provide palatable, stable and effective treatment for sore throats.

Example 2

In a similar manner to that described in Example 1 above, lozenges were made containing the sodium salt of diclofenac (6.25 milligrammes per lozenge).

Example 3

In a similar manner to that described in Examples 1 above, lozenges were made containing piroxicam (20 milligrammes per lozenge).

Example 4

In a similar manner to that described in Example 1 above, lozenges were made containing indomethacin (6.25 milligrammes per lozenge).

Example 5

A mixture of an NSAID, sorbitol and glycerin was dissolved in aqueous alcohol to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered manually-operated spray mechanism which enables the formulation to be sprayed on to the mucous membrane of the throat as a fine spray.

Example 6

A pharmaceutical lozenge formulation is prepared containing the following components expressed in milligrams per lozenge.

Ketoprofen	q.v.
Calcium Carbonate	7.5
Polyvinylpyrrolidine	1.43
Colloidal Silicon Dioxide (Aerosil)	0.036
Magnesium Stearate	0.18
Isomalt	1885
Lycasin	440
Flavouring	q.v.

The ketoprofen and calcium carbonate are blended for two minutes and the blend granulated with a solution of the polyvinylpyrrolidine in isopropanol. The granules are dried and the colloidal silicon dioxide and magnesium stearate are added and the resulting mixture blended for five minutes. A molten lozenge base is prepared by dissolving the isomalt in the minimum amount of water. The lycasin is added and the mixture heated at 110-120°C. The mixture is then heated to 145°C under vacuum to remove water to give the molten lozenge base. The blended granule and the flavourings are then added to the molten lozenge base. The resulting mixture is cooled and formed into a continuous cylindrical mass from which individual lozenges are prepared.

In a similar manner to that described above in Example 6 lozenges containing diclofenac, piroxicam and indomethacin can be prepared.

Examples 7 to 12

The NSAID will be present in the compositions of Examples 7 to 12 at the dose which will be known by those skilled in the art as appropriate for the NSAID concerned. The component identified in Examples 7 to 9 as "Active ingredient" can be any one or more of the one or more active ingredients

selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, minerals and vitamins, particularly any one or more of the compounds specifically identified hereinbefore.

Example 7

Lozenges are prepared containing the following ingredients expressed as the weight in milligrammes per lozenge.

NSAID	qv
Calcium Carbonate	7.5
Active ingredient	q.v.
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350

The mixture of the sugar and liquid glucose is heated to 140° and a vacuum applied to reduce the water content of the mixture. The flavouring is added in a sealed vessel. The flurbiprofen, the active ingredient and the calcium carbonate are blended and the blend added to the remainder of the ingredients. The resulting mixture is cooled and formed into a continuous cylindrical mass from which the individual lozenges are formed. The individual solid lozenges are visually inspected and then packed.

The resulting lozenges provide palatable, stable and effective treatment for the symptoms of colds and flu particularly including sore throats.

In the manner described above lozenges containing combinations of the active ingredients with ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin can be prepared.

Example 8

A mixture of an NSAID, the active ingredient, sorbitol and glycerin is dissolved in aqueous alcohol to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered manually-operated spray mechanism which enables the formulation to be sprayed on to the mucous membrane of the throat as a fine spray.

Example 9

A pharmaceutical lozenge formulation is prepared containing the following components expressed in milligrams per lozenge.

NSAID	q.v.
Calcium Carbonate	7.5
Active ingredient	q.v.
Polyvinylpyrrolidine	1.43
Colloidal Silicon Dioxide (Aerosil)	0.036
Magnesium Stearate	0.18
Isomalt	1885
Lycasin	440
Anethole	q.v.

The NSAID, the active ingredient and calcium carbonate are blended for two minutes and the blend granulated with a solution of the polyvinylpyrrolidine in isopropanol. The granules are dried and the colloidal silicon dioxide and magnesium stearate are added and the resulting mixture blended for five minutes. A molten lozenge base is prepared by dissolving the

isomalt in the minimum amount of water. The lycasin is added and the mixture heated at 110-120°C. The mixture is then heated to 145°C under vacuum to remove water to give the molten lozenge base. The blended granule and the anethole are then added to the molten lozenge base. The resulting mixture is cooled and formed into a continuous cylindrical mass from which individual lozenges are prepared.

In the manner described above in Example 9 lozenges containing combinations of the active ingredients with ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin can be prepared.

Example 10

Lozenges are prepared containing the following ingredients expressed as the weight in milligrammes per lozenge.

NSAID	q.v.
Flavouring (orange)	1.645
Flavouring (grapefruit)	3.75
Calcium Carbonate	7.5
Anethole	5.184
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350

The mixture of sugar and liquid glucose is heated to 140°C and a vacuum applied to reduce the water content of the mixture. The flavouring is added in a sealed vessel. The flurbiprofen and calcium carbonate are blended and the blend and flavourings are added to the remainder of the ingredients. The resulting mixture is cooled and formed into a continuous cylindrical mass from which the individual lozenges are formed. The individual solid lozenges were visually inspected and then packed.

The resulting lozenges provide palatable, stable and effective treatment for sore throats.

In the manner described in Example 10 above lozenges containing anethole with ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin can be prepared.

Example 11

A mixture of an NSAID, anethole, sorbitol and glycerin is dissolved in aqueous alcohol to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered manually-operated spray mechanism which enables the formulation to be sprayed on to the mucous membrane of the throat as a fine spray.

Example 12

A pharmaceutical lozenge formulation is prepared containing the following components expressed in milligrams per lozenge.

NSAID	q.v.
Calcium Carbonate	7.5
Polyvinylpyrrolidine	1.43
Colloidal Silicon Dioxide (Aerosil)	0.036
Magnesium Stearate	0.18
Isomalt	1885
Lycasin	440
Anethole	q.v.

The flurbiprofen and calcium carbonate are blended for two minutes and the blend granulated with a solution of the polyvinylpyrrolidine in isopropanol. The granules are dried and the colloidal silicon dioxide and magnesium stearate are added and the resulting mixture blended for five minutes. A molten lozenge base is prepared by dissolving the isomalt in the minimum amount of water. The lycasin is added and the mixture heated at 110-120°C. The mixture is then heated to 145°C under vacuum to remove water to give the molten lozenge base. The blended granule and the anethole are then added to the molten lozenge base. The resulting mixture is cooled and formed into a continuous cylindrical mass from which individual lozenges are prepared.

In the manner described above in Example 12 lozenges containing anethole with ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin can be prepared.

The effectiveness of the treatment can be demonstrated by means of clinical trials in which patients suffering from sore throats are administered the formulations described in any one of the Examples or a placebo. The patient is asked to assess the effectiveness of the treatment on parameters such as the relief of the pain associated with the sore throat, the reduction in the swelling of the throat and/or the improvement in swallowing following treatment. The patients are also examined by a clinician to determine the amount of tonsillopharyngitis.

Claims

1. The use of an NSAID selected from ketoprofen, diclofenac, piroxicam and indomethacin for the preparation of a medicament in the form of a masticable or suckable solid dosage form or a liquid or a spray intended to release a therapeutically effective amount of the NSAID in the oral cavity so as to deliver the NSAID to the surface of the throat for the treatment of sore throat.

2. A method of treating a sore throat comprising the administration of a therapeutically effective amount of an NSAID selected from ketoprofen, diclofenac, piroxicam and indomethacin to the surface of the sore throat from a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or a spray.

3. A use or method as claimed in any preceding claim wherein the amount of the NSAID is from 2.5 to 25 mg per unit dose.

4. A use or method as claimed in claim 4 wherein the amount of the NSAID is from 5 to 12.5 mg per unit dose.

5. A pharmaceutical composition comprising a combination of a therapeutically effective amount of an NSAID selected from ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin with (a) therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat in the form of a masticable or suckable solid dosage form or a liquid or spray

intended to release a therapeutically effective amount of the NSAID and any active material present in the oral cavity so as to deliver the NSAID to the surface of the throat for the treatment of sore throat.

6. A method of treating a sore throat comprising the administration of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a liquid or spray, said pharmaceutical composition comprising a combination of a therapeutically effective amount of an NSAID selected from ibuprofen, flurbiprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin with (a) a therapeutically effective amount of one or more active ingredients selected from an antihistamine, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, a centrally acting analgesic, a local anaesthetic, an antibacterial compound, an antiviral compound, an antibiotic compound, an antifungal compound, minerals and vitamins and/or (b) a burn-masking amount of an agent which has a warming effect on the mucosa of the throat to the surface of the sore throat

7. A composition or method as claimed in claim 5 or claim 6 wherein

the antihistamines is selected from acrivastine, azatadine, buclizine, cetirizine, cinnarizine, clemastine, loratidine and pharmaceutically acceptable salts thereof;

the cough suppressant is selected from codeine, dextromethorphan or pholcodine and pharmaceutically acceptable salts thereof.

the decongestant is selected from pseudoephedrine, phenylpropanolamine and phenylephrine and pharmaceutically acceptable salts thereof.

the expectorant is selected from acetylcysteine, ammonium chloride, carbocysteine, guaifensin and potassium citrate,

the muscle relaxant is methocarbamol,

the centrally acting analgesic is selected from codeine and its salts and hydrocodone.

the local anaesthetics is selected from benzocaine, lignocaine, mepivacaine, prilocaine, and pharmaceutically acceptable salts thereof.

the antibacterial compounds is selected from amylmetacresol, dichlorobenzyl alcohol, quaternary ammonium compounds such as cetrimide, or benzalkonium chloride.

the antiviral compounds is selected from zinc salts (for example the acetate, gluconate and ascorbate salts), acyclovir and its sodium salt.

the antibiotic compound is metronidazole.

the antifungal compound is selected from nystatin, amphotericin, miconazole and fluconazole.

the mineral is selected from zinc and selenium salts and

the vitamin is selected from vitamins A, C, D, E and K, sodium ascorbate, riboflavine and thiamine hydrochloride.

8. A composition or method as claimed in any one of claims 5 to 7 wherein the amount of the NSAID is from 2.5 to 200 mg per unit dose.

9. A composition, use or method as claimed in any preceding claim in which the warming agent contains or consists of anethole.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 07412 A (VIRGINIA COMMONWEALTH UNIVERSITY) 14 March 1996 see claims see page 12, line 25 - page 13, line 23	1-9
Y	WO 94 13280 A (MAYOR) 23 June 1994 see the whole document	1-9
Y	WO 91 02512 A (SEPRACOR) 7 March 1991 see the whole document	1-9
Y	US 5 567 733 A (J.G.DISHLER) 22 October 1996 see the whole document	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date .

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
29 September 1998	08/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/EP 98/03179

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 23591 A (PROCTER & GAMBLE) 8 September 1995 see claims see examples	1-9
Y	DATABASE WPI Week 9211 Derwent Publications Ltd., London, GB; AN 92-084353 '11! XP002078972 see abstract & JP 04 026618 A (JAPAN TOBACCO INC.,JP) 29 January 1992	1-9
Y	DATABASE WPI Week 8822 Derwent Publications Ltd., London, GB; AN 88-149738 '22! XP002078973 see abstract & JP 62 298528 A (MIZUSHIMA H.) 25 December 1987	1-9
Y,P	WO 97 18802 A (BOOTS) 29 May 1997 see the whole document	1-9
Y,P	WO 97 38663 A (FLEMINGTON) 23 October 1997 see the whole document	1-9
Y,P	WO 97 38662 A (FLEMINGTON) 23 October 1997 see the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/EP 98/03179

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/03179

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 2 & 6
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ..al Application No
PCT/EP 98/03179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523591 A		EP 0748212 A	18-12-1996
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